JAMBI MEDICAL JOURNAL
Jurnal Kedokteran dan Kesehatan
Vol. 13 No 1 May 2025
DOI: 10.22437/jmj.v13i1.29561
Journal homepage: https://online-journal.unja.ac.id/kedokteran
p-Issn : 2339-269x
e-Issn : 2580-6874

Review

# Stem Cell As A Promising Modality In Chronic Kidney Disease Children Future Treatment

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**Article History:**
Submit : December 2023
Accepted: March 2025

**Keyword:**
Chronic Kidney Disease;
Prevention;
Treatment;
Urid Acid Levels;
Stem Cell



## ABSTRACT

**Background:** End-stage kidney disease (ESKD) is the origin of chronic kidney disease (CKD), both in adults and children. The progression of CKD to ESKD often cannot be prevented, even with sophisticated and up-to-date medicines.
**Method:** Data search was conducted by searching for articles in electronic databases, namely PubMed, ScienceDirect, Scopus, Cochrane and Google Scholar.
**Result:** Based on the pathophysiology, the transformation from CKD to ESKD involves a process of fibrosis in the kidneys, which is extensive and persistent. Several studies in experimental animals have found that treatment with stem cells in liver cells can repair cells that have experienced fibrosis, this may be analogous to fibrosis in the kidneys. Through this library extract, we will discuss stem cells, as well as how to treat stem cells for CKD and ESKD in the future.
**Conclusion:** There are various variations in research results on the effectiveness of stem cell therapy in CKD patients. This occurs because of differences in the baseline clinical entity of CKD. Research on stem cell therapy in children has not been well published.

## INTRODUCTION

Chronic kidney disease (CKD) is a big problem in the field of child health, not only in Indonesia, but also in the world. The incidence of CKD is increasing, causing the quality of life of children and adults of productive age to decline, even contributing to mortality related to non-communicable diseases or what we know as non-communicable diseases (NCDs). CKD is a condition that describes kidney damage that lasts at least three months with or without a decrease in glomerular filtration rate (GFR). The decline or loss of kidney function occurs gradually, is irreversible, and can progress to end-stage kidney disease (ESKD).[1-4]

The incidence of CKD in children in Europe is around 11 – 12 per million population, while the prevalence reaches 55 – 60 per million population.[1] In the United States, the incidence of ESKD reaches 12.9 per million population/year at the age of 0 – 19 years.[5] The epidemiology of CKD in children is more focused on children who are already in the ESKD stage who need kidney replacement therapy. The incidence and

prevalence of CKD in children is greater in boys than girls due to the high frequency of congenital abnormalities of the kidney and urinary tract (CAKUT) in boys.[1,2] According to research conducted at the Dr. National Central General Hospital Cipto Mangunkusumo (RSCM), there were 150 cases of CKD in 2007 – 2009.[6]

Chronic kidney disease is a term that was first put forward by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002. The term CKD is used to replace chronic kidney insufficiency because the term CKD can describe the severity of CKD which requires different treatment at each stage.[7]

As it progresses. time, in 2012 Kidney Disease Improving Global Outcomes (KDIGO) further refined the classification of CKD stages in order to optimize the treatment of CKD sufferers.[8] A child suffering from CKD will gradually experience progression to a more severe condition in the form of ESKD.[9]

In this condition, damage to the glomerulus and kidney tubules occurs, resulting in a decrease in kidney function. The current management is to prevent the progression of kidney damage and maintain it as long as possible by carrying out correct conservative management and kidney replacement therapy or what we know as kidney replacement therapy (KRT). Thus, other alternatives are needed for kidney failure therapy. At the end of this decade a new strategy was discovered in the therapy of kidney failure, namely the development of stem cells from extracellular vesicles. This method is considered capable of regenerating kidney cells so that it can be used as an alternative in kidney failure therapy. This literature extract was created to learn more about the treatment modalities that will be developed in the future, namely stem cell therapy or what we know as stem cells in children with CKD.

## METHOD

The study was a scoping review, data search was conducted by searching for articles in electronic databases, namely PubMed, ScienceDirect, Scopus, Cochrane and Google Scholar. The keywords used in this study were "(Stem cell) OR (mesenchymal stem cell) AND (chronic kidney disease) OR (renal insufficiency) AND (children) OR (pediatric)" in PubMed, Scopus, ScienceDirect, Cochrane, and Google Scholar.

The article selection process was carried out in several stages. First, article identification was carried out based on a search in the database. Second, duplicate articles were screened. Third, articles were screened based on title and abstract. Fourth, articles that passed the initial selection were further analyzed with a full-text evaluation to ensure suitability with the research topic. Finally, articles that met all criteria were synthesized to support this scoping review.

## RESULTS

### Chronic kidney disease

### Definition

Chronic kidney disease (CKD) is a term used to replace chronic kidney failure with the aim of detecting it as early as possible, so that its progression can be prevented. Based on the 2002 Kidney Disease Outcome Initiative (KDOQI) guidelines, CKD is kidney disease with damage for at least 3 months with or without a decrease in glomerular filtration rate (GFR). In 2012, The Kidney Disease: Improving Global Outcome (KDIGO) updated the definition to include abnormalities in kidney structure and function that have persisted for more than 3 months, with implications for health.[8] The criteria for CKD based on KDIGO are explained in (Table 1).[8].

**Table 1**. *CKD criteria*

| Criteria | Description |
|---|---|
| Marker of kidney damage | Albuminuria (AER ≥ 30 mg/24 hours, ACR ≥ 30 mg/gram)<br>Urine sediment abnormalities<br>Electrolyte and other disorders due to tubular disorders<br>Visible abnormalities on histology<br>Structural disturbances visible on imaging<br>History of kidney transplantation |
| Decrease in GFR | GFR < 60 mL/menit/1,73 $m^2$ (G3a – G5) |

ACR, *albumin-creatinine ratio*; GFR, Glomerular filtration rate
**Source: KDIGO 2012[8]**

The addition of the sentence "there are implications for health" aims to emphasize that there are many abnormalities in kidney structure and function, but not all of them are detrimental to health so this needs to be stated explicitly. A duration of illness of three months was used to differentiate between the acute and chronic phases. This makes it easier for clinicians to think about the differences in etiology, intervention and outcome of the disease.[8] The Kidney Disease: Improving Global Outcome (KDIGO) classifies CKD based on GFR and albuminuria. Classification is explained in (Table 2)8 and (Table 3).[8]

***Table 2.*** *CKD classification based on GFR*

| Stage | GFR (mL/minutes/1,73 $m^2$) | Interpretation |
|---|---|---|
| G1 | ≥ 90 | Normal or high |
| G2 | 60 – 89 | Mild decrease |
| G3a | 45 – 59 | Low-intermediate decrease |
| G3b | 30 – 44 | Intermediate-high decrease |
| G4 | 15 – 29 | Severe decrease |
| G5 | <15 | End-stage kidney disease |

**Source: KDIGO 2012[8]**

**Table 3.** CKD classification based on albuminuria

| Stage | Albumin exretion rate (mg/24 hours) | Albumin/creatinine ratio (mg/mmol) | (mg/g) | Description |
|---|---|---|---|---|
| A1 | < 30 | < 30 | < 30 | Normal or slightly increase |
| A2 | 30 – 300 | 30 – 30 | 30 - 300 | Moderate increase |
| A3 | › 300 | › 300 | › 300 | Very increase |

**Source: KDIGO 2012[8]**

The CKD classification based on GFR in KDIGO 2012 has been increased to G3a and G3b, because these two stages have different outcomes and risks. Stage G3b has a higher mortality rate and risk of cardiovascular complications than stage G3a.[8]

The addition of albuminuria as one of the staging criteria for CKD has several reasons, namely: 1) albumin is the main component of urine protein in kidney disease so the latest recommendation for measuring urine protein is to measure urine albumin levels; 2) the latest epidemiological data from studies around the world show an association between the amount of albumin in the urine and the risk of cardiovascular disease.[8]

Children who suffer from CKD will experience progression to a more severe

condition in the form of kidney failure. Therefore, efforts must be made to ensure that the course of the disease becomes more severe as long as possible by carrying out correct conservative management.[8.9]

**Causes**

The etiology of childhood CKD varies according to age and race. The most common etiology of pediatric CKD is CAKUT at 50%, and usually occurs in children aged <12 years, followed by hereditary nephropathy and glomerulonephritis which usually occurs in children aged >12 years. This is different from the etiology of adult CKD which is dominated by diabetic nephropathy, hypertension and hereditary polycystic kidney disease.[4,10]

**Pathogenesis**

In principle, the pathogenesis of kidney failure can occur due to damage to the glomerulus and interstitial tubular damage. Damage to the glomerulus is divided into 2, namely genetic factors and acquired factors which include the immune system and systemic diseases.[11,12] The mechanism of genetic damage is caused by mutations in the COL4A5 gene for collagen synthesis. The glomerular damage caused by genetics is Alport syndrome. This causes an irregular shape of the glomerular basement membrane (GBM) accompanied by separation and thickening of the layers, causing glomerulosclerosis.[11,12]

Glomerular damage due to acquired factors is caused by damage to the immune system, metabolism (diabetes), and mechanical stress. Acquired glomerular damage is divided into three groups, namely non-proliferative, proliferative, and systemic disease. In non-proliferative mechanisms, glomerular damage is not accompanied by glomerular inflammation and without immunoglobulin deposits such as focal segmental glomerulosclerosis (FSGS). This causes damage to the podocytes. In proliferative glomerular damage, accompanied by immunoglobulin deposits or glomerular inflammation such as IgA nephropathy, lupus nephritis. Immune complex deposits in the kidneys cause intrinsic cell activation in kidney cells through complement activation thereby stimulating inflammatory cells which release cytokines, proteases, chemokines and inflammatory mediators.[11,12]

Immune complexes can deposit in mesangial cells or under the renal epithelium. The inflammatory process occurs when inflammatory cells circulating in the blood interact with immunoglobulins produced by intrinsic cells of the kidney. Therefore, antibody deposits in mesangial and epithelial cells can activate mesangial cells to produce and call leukocytes and platelets. Leukocytes can produce cytokines, lysosomal enzymes, reactive oxygen species (ROS) which can damage the walls of blood vessels in the kidney glomerulus. Inflammation of the glomerulus can resolve completely or be accompanied by fibrosis.[11,12]

Damage to kidney structure can also be caused by systemic diseases such as hypertension and diabetes. Systemic hypertension can cause hemodynamic changes in blood pressure in the glomerulus, causing glomerular hypertension and causing injury to the glomerulus. Under normal circumstances, blood pressure in the kidneys is regulated automatically (autoregulation). Chronic hypertension can cause arterial vasoconstriction and sclerosis and over time glomerular and tubular interstitial atrophy can occur. Several factors also play a role in myointimal proliferation and vascular wall narrowing. Meanwhile, chronic glomerular hypertension can increase the production of extracellular matrix (ECM) by mesangial cells, resulting in glomerulosclerosis.[11,12]

The second process is damage to the tubular interstitial. Glomerular damage can impact the tubular interstitial. This is because the tubular cells are exposed to substances they should not be because the glomerulus loses its ability to filter so that the tubular cells become injured and inflamed. In

addition, damage to the interstitial tubules can occur due to the presence of inflammatory cells due to activation of inflammatory mediators, increased interstitial fibroblasts due to increased proliferation and decreased apoptosis of interstitial cells, accumulation of ECM due to increased ECM synthesis components and decreased ECM degradation, tubular atrophy due to apoptosis and epithelial-mesenchymal transdifferentiation (EMT) as well as narrowing of the peritubular capillaries so that the kidneys can experience ischemia.[11,12]

**Conservative treatment**

Conservative therapy or predialysis therapy aims to slow down the process of kidney damage and improve the imperfect function of kidney hemeostasis. Conservative therapy consists of regulating food, improving nutritional status, controlling metabolic disorders and the emergence of uremia symptoms. The most difficult challenges in conservative therapy lie in aspects of nutrition and growth, anemia management and psychosocial aspects.[8,13]

**Kidney replacement therapy**

Kidney replacement therapy consists of two large groups: (1) Natural kidney replacement therapy, which we know as kidney transplantation, and (2) Artificial kidney replacement therapy, consisting of hemodialysis, peritoneal dialysis and hemodiafiltration. The treatment for every pediatric ESKD patient is a kidney transplant, but the process to get there requires an artificial TSG first, so that hemodynamics and quality of life are maintained. Therefore, most patients undergo dialysis first as a replacement for kidney function.[22] From an ethical point of view, life-saving therapy such as TSG should be available to all CKD patients, but there are limitations in several ways, making it difficult to implement.[8]

At the end of this decade a new strategy was discovered in ESKD therapy, namely the development of stem cells from extracellular vesicles. This method is considered capable of regenerating kidney cells so that it can be used as an alternative to ESKD therapy.[14-16]

**Stem cell**

Stem cells are cells that have the potential to differentiate and regenerate into various cell formation pathways. Stem cells can be found in all parts of our body, from the beginning of development to the end of life. Stem cells regenerate themselves through the process of mitosis and differentiate into various types of specific cells. These cells can develop, grow, maintain and repair if there is damage to organs.[17]

In terms of potential (ability to differentiate), stem cells are classified into 4 important parts, namely totipotent, pluripotent, multipotent and unipotent. Based on the source, stem cells are divided into early stem cells which are better known as embryonic stem cells (ESC) and mature or adult stem cells. There are three main types of stem cells, namely ESC, adult stem cells, and induced pluripotent stem cells (iPSC).[17,18]

Embryonic stem cells originate from the embryo before the implantation process in the uterus, during the blastocyst period, when the embryo is 4 or 5 days of development. These cells have pluripotency and have great potential as a therapeutic. Greater therapeutic potential than adult stem cells. Adult stem cells can be found in the body after embryonic development, but are limited by the origin of the cells. This type of stem cell is characterized by the ability to regenerate and differentiate into certain types of tissue. Adult stem cells can be found in certain body tissues including skin, muscle, intestines and bone marrow, including the baby's umbilical cord and placenta.[18]

Induced pluripotent stem cells are a reprogramming of somatic cells back into a pluripotent state or embryonic-like cell, using the expression of certain genes. Just like ESC, iPCS has enormous therapeutic potential.[16-18] Types of stem cell transplantation are divided into 2, namely:

1. Autologous

This procedure uses stem cells that come from the patient himself. This procedure is highly recommended because the risk of rejection from the body's immune system is lower.

2. Allogenic

This procedure uses stem cells that come from another person. To avoid complications due to rejection by the immune system, it is necessary to carry out a compatibility test first.

The goal of stem cell therapy is to repair damaged tissue that cannot heal. Research on stem cells gives hope to patients who do not receive treatment to cure their disease only to relieve the symptoms of the patient's chronic disease. Stem cell therapy involves more than just transplanting cells into the body and creating the growth of new and good tissue.[17]

A number of stem cell therapies are still in the experimental stage and are expected to be able to treat various diseases such as cancer, type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac disease, heart failure, muscle damage and neurological disorders. Researchers also have high hopes for the development of stem cell therapy.[17]

Some adult stem cells that can be used in therapy include hematopoietic stem cells (which are used in hematologic disorders) which are found in the bone marrow, mesenchymal stem cells (MSC) which can be found in the bone marrow, muscles, blood vessels and fatty tissue. Mesenchymal stem cells can differentiate into osteoblasts, chondrocytes and adipocytes. Thus, MSCs can be widely used in therapeutic applications when compared to other adult stem cells. The MSC mechanism in repairing and maintaining tissue is the role of paracrine activity which secretes proteins/peptides and hormones, transfers mitochondria via microvesicles, and transfers exosomes or microvesicles containing RNA and other molecules.[19]

The type of MSC most researched currently is MSC which comes from the bone marrow and is given intravenously. Autologous stem cells (cells that come from the same individual) are more recommended than allogenic stem cells (cells that come from different individuals) because the immune rejection reaction is lower. The optimal dose for MSC therapy to function optimally is still a matter of debate. Macrophages can attack and eliminate (mesenchymal stem cell extracellular vesicles) the given MSC-EVs so a higher dose is needed to get maximum results. However, larger doses are not always associated with significant improvement in outcomes. Low (1x105 cells/kg) and high doses (2.5x106 cells/kg) can also increase blood flow and perfusion to the kidneys in kidney failure.[16,20]

Clinical trial research related to MSCs in hematological diseases, organ transplants, lung, liver, bone, heart, nerve and autoimmune diseases has been carried out. The clinical trial carried out on this disease was phase I – II with the results requiring further research to determine the efficiency of MSC therapy. Phase I or II studies conducted on autoimmune patients such as systemic lupus erythematosus (SLE) stated that there was an increase in the disease activity index score and a decrease in autoreactive antibodies in the blood and there were no side effects after one year of follow-up.[21] Research on MSC therapy has also been carried out. conducted on the heart, showed that MSCs can repair damage to the myocardium, reduce structural changes in the left ventricle, and regenerate the myocardium. Clinical trials in neurological diseases show that MSCs can improve neurological function after tissue damage occurs.[18]

Apart from these diseases, stem cell therapy in liver cirrhosis sufferers is quite promising. In animals with liver fibrosis, injection of MSCs has been shown to be able to bind to liver cells in these animals and prevent further fibrosis. In addition, MSCs

reduce inflammatory processes and fibrosis formation activities, prevent hepatocyte apoptosis, stimulate liver cell proliferation and stimulate collagen degradation.[22]

Apart from the ability of stem cells to regenerate damaged cells, it is necessary to pay attention to the risks that can occur related to their use. The risk that can arise from the use of stem cells is the formation of tumors. Stem cells have several characteristics in common with cancer cells, such as growth regulation, resistance to apoptosis and the ability to replicate quickly and over a long period of time. The potential of stem cells themselves (pluripotent or multipotent) is an important factor that contributes to tumor formation. The use of pluripotent stem cells such as ESC and iPCS may cause teratoma. Autologous stem cells can also be a risk factor for tumor formation and can metastasize to other organs. However, according to research that has been carried out, the results showed that intravenous administration of adult stem cells such as MSCs was not followed by tumor formation even though follow-up was not carried out in the long term to see if side effects occurred. Patients who receive bone marrow or organ donors also have a higher risk of experiencing malignancy.[17,18]

The use of stem cells as therapy can also have an effect on the body's immune system. MSC cells have lower immunogenic potential and are safer compared to other stem cells. Mesenchymal stem cells can inhibit T cell proliferation, inhibit monocyte differentiation, and inhibit cytokine production. However, if dysfunction occurs or is given in an inappropriate location, the immune system can activate and damage the stem cells. Immunosuppressants can be given to minimize the risk of unwanted reactions, but they can trigger drug-related side effects.[17,18]

**The role of stem cell in chronic kidney disease**

Chronic kidney disease can progress to ESKD, due to a prolonged inflammatory response, followed by fibrosis and progressive loss of function. The main therapy for ESKD is kidney replacement therapy (KRT), either artificially in the form of dialysis, and the best is kidney transplantation. Apart from being very expensive and still having complications, finding a suitable kidney for the patient is very difficult.[14]

In recent years, MSCs have been widely used in research models for CKD therapy. Mesenchymal stem cells are cells such as fibroblasts that have the ability to regenerate themselves and differentiate into various types of mesoderm cells such as osteoblasts, adipocytes and chondrocytes. Mesenchymal stem cells can be found in bone marrow, fat tissue, blood, placenta and umbilical cord. Based on research that has been carried out, MSCs inhibit apoptosis and increase tubular cell proliferation which can repair damaged kidneys. The use of MSCs can also suppress inflammatory processes in the kidneys, reduce fibrosis and glomerulosclerosis.[14,15,20,21]

Mesenchymal stem cells have the ability to migrate to damaged tissue which is called "homing". When tissue damage occurs, MSCs will pass through the endothelium and go to the damaged tissue. This can happen because there are compounds released by damaged tissue such as chemokines and matrix metalloproteinase (MMP) which can be received by MSC.[14-16,18]

The mechanism underlying this is because MSCs have a secretome, which is a substance consisting of growth factors, cytokines, and extracellular vesicles (EVs) which can repair damaged tissue and reduce inflammation. Apart from that, MSCs have (1) immune system signals in the form of IL-6, IL-8, and TGF b, (2) substances related to the extracellular matrix such as tissue inhibitor of metalloproteinases 2 (TIMP-2), fibronectin, collagen and ( 3) growth factors such as insulin-like factor1 (IGF-1), hepatocyte growth factor (HGF), and vascular endothelial growth factors (VEGF). These

factors can increase cell repair and epithelial proliferation in the kidney. Extracellular vesicles (EVs) can prevent the progression of kidney damage. Extracellular vesicles can influence several types of cells for proliferation, angiogenesis, and immune processes. According to research conducted by Belingheri et al, it is stated that administering MSC is safe and can be tolerated well by the body.[14-16,18]

From the research that has been conducted, adult stem cells have the best effectiveness for CKD therapy. Research on mice that carried out Adriamycin (ADR)-induced nephropathy experienced migration and loss of podocytes, the formation of synectia and the formation of glomerular fibrosis. Then given re-marrow MSCs, the glomerular structure experienced significant changes, so that the glomerulosclerosis tissue was reduced. However, this therapy did not improve proteinuria. Other studies state that there is a gradual improvement in urea and creatinine values along with the amount of bmMSC administered. Another study stated that after follow-up, samples given MSC did not experience improvement in kidney function.[21]

## CONCLUSION

Chronic kidney disease in children has long-term consequences, namely that it can develop into ESKD. Effective therapy to prevent the progression of chronic kidney disease from progressing to ESKD needs to be developed. Renal regenerative therapy through stem cells is a therapeutic modality that is expected to prevent kidney failure from progressing to a further stage. The use of stem cells in ESKD is theoretically very useful, but further research needs to be done to assess the possibility and effectiveness of therapy in preventing the progression of CKD to ESKD. As an initial step, what is needed is protein profiling which is the key to targeting stem cell therapy, in order to prevent CKD from becoming ESKD. After that, research continued with stem cell therapy targeting these proteins. After research with experimental animals, clinical trials can be carried out using randomized control trials.

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